UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/733,306	12/08/00	SCHWARZ	M 9022-20

020792
MYERS BIGEL SIBLEY & SAJOVEC
PO BOX 37428
RALEIGH NC 27627

HM12/1106

EXAMINER	
SCHMIDT,M	
ART UNIT	PAPER NUMBER
1635	9

DATE MAILED: 11/06/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)
	09/733,306	SCHWARZ, MARGARET ...
	Examiner	Art Unit
	Mary Schmidt	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely ... after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days ...
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the ...
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. ...).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely ... earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5
4)☐ Interview Summary (PTO-413) Paper No. ...
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other

DETAILED ACTION

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. The specification as filed discloses sequences which are not identified by sequence identifiers.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1 is drawn to methods of facilitating vascular growth in cardiac muscle of a subject in need of such treatment comprising inhibiting EMAPII activity in said subject by an amount effective to stimulate vascular growth in said cardiac muscle. Claim 3 specifies wherein the

compound is an antisense. Claim 4 is drawn to a method according to claim 1 wherein said inhibiting step is carried out by downregulating EMAP II expression. Claim 5 specifies using an antisense to downregulate EMAP II expression. Claim 6 specifies administering any EMAP II receptor antagonist. Claims 11-19 similarly are drawn to methods of decreasing EMAPII via an antibody, an antisense or a receptor agonist.

Although Applicant's elected antibody as the elected species, in view of the 35 U.S.C. 112, rejection, it is not considered an undue burden to examine antisense and agonists as well.

There is a high level of unpredictability in the art for any method of treatment with a therapeutic agent for treating a disease or causing a particular physiological condition when the cite of action of the pharmaceutical composition is not clear, when the target site is not readily accessible or the compound does not readily find the target of action, and when the action of the pharmaceutical composition on other parts of the whole organism are unknown.

For instance, in the antisense art is unpredictable to design any antisense to a target gene for use in therapeutic situations since the factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such

that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (in vivo) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)."

In vitro, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." And in the instant case, the claims read broadly on administration of an antisense inhibitor in any cell, therefore the whole organism included. While the specification teaches cell culture inhibition, no evidence of successful *in vivo* (whole organism) antisense inhibition has been shown, nor do the culture examples correlate with whole organism delivery.

One of skill in the art would not accept on its face the successful delivery of any antisense molecule to EMAPII *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in

whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed for design of antisense and delivery to whole organisms for the claimed functions.

Furthermore, although the antibody art is more established, and antibodies to EMAPII are known in the art (see IDS reference 1, for instance), one skilled in the art would necessarily practice undue experimentation to use such antibodies, or to make and use other antibodies to EMAPII for the claimed functions in any whole organism, facilitating vascular growth in cardiac muscle. Neither the specification nor the art teach a nexus for administration of any EMAPII antibody to a whole organism for the claimed functions. Specifically, the factors considered unpredictable are (1) dosage, (2) site of action, (3) routes of administration, and (4) toxicity, such that one skilled in the art would be able to make and use the invention as claimed. If the necessary site of action for EMAPII is inside the cardiac muscle cell, it is unpredictable that an antibody would be able to enter the cell to act on the target protein. Similarly, one skilled in the

art would necessarily practice "trial and error experimentation" to use any antibody to EMAPII in any whole organism for the methods of treatment claimed.

One skilled in the art would further need to practice undue experimentation to design any EMAPII antagonist for use as a whole organism therapeutic agent as broadly claimed. Although *in vitro* methods for screening for antagonists to EMAPII were known in the art, methods of using any such identified antagonist *in vitro* for the therapeutic uses claimed would require one skilled in the art to practice "trial and error" experimentation for the reasons argued above for design of functional antisense and antibodies for whole organism use. Specifically, it would be unpredictable to ascertain unpredictable factors such as dosage, site of action, formulation (including stability *in vivo* of the administered compound), routes of administration and toxicity based on *in vitro* results since in vitro results do not take into account the unpredictable factors *in vivo*. Further, there is no general guideline for any whole organism administration of any possible antagonist since the mechanism for action of such pharmaceutical compositions varies greatly within one species, often with an unknown amount of side effects, thus lending researchers to practice administration of test compounds in animal models first. Even so, animal models are not indicative of any whole organism success in most studies since the physiology of an animal model usually does not correlate to any whole organism use. For these reasons, one skilled in the art would necessarily practice an undue amount of experimentation to make and use the invention claimed for methods of facilitating vascular growth in cardiac muscle via antagonism of either EMAPII gene or protein function.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.

SEAN McGARRY
PRIMARY EXAMINER

M. M. Schmidt
September 14, 2001